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TITLE: A Nationwide Population-Based Approach to Study Health-Related and Psychosocial Aspects of Neurofibromatosis Type 1

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14. ABSTRACT Using the unique resources for conducting epidemiological research in Denmark, we are carrying out seven studies in this research project with the overall objective of evaluating health-related and psychosocial aspects of NF1 in a large population-based setting. Studies 1-5 are register-based studies, study 6 a questionnaire study, and study 7 an interview study.

Within the second year, 1) we accomplished to prepare all patient material for study 6 and 7 and to apply for permission from the Human Research Protection Office (HRPO) for final US approval to conduct these two studies, 2) to select the population comparison group, 3) to send the cases (NF1 patients) and the population-based comparison cohort to the State Serum Institute and Statistics Denmark to obtain individual-level data on all outcomes data needed to analyze the register-based studies (studies 1-5), 4) to have a final dataset ready for analyses for the register-based studies (studies 1-5), 5) to start up analyzing and drafting the manuscript for study 1, 6) and to start up drafting the manuscript for study 5.

15. SUBJECT TERMS
Neurofibromatosis type 1, population-based, nation-wide, clinical epidemiology, somatic disease, mental disease, cohabitation, educational attainment, psychosocial burden, patient-reported outcomes, neuropsychological assessments

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1. INTRODUCTION

Using the unique resources for conducting epidemiological research in Denmark with personal identification numbers for all citizens and the existence of a number of unique population-based, nationwide administrative registries, we suggest carrying out seven studies with the overall objective of evaluating health-related and psychosocial aspects of NF1 in a large population-based setting. The study cohorts consist of a *clinical* NF1 cohort of patients affiliated to the two national Centers for Rare Diseases (CRD) and a *register-based* cohort of all patients hospitalized for or with existing NF1 in Denmark as well as a large population-based comparison cohort. The specific aims are:

- to screen for somatic (study 1) and psychiatric disease (study 2) throughout the different phases of life as well as to assess the risk of adverse pregnancy outcomes (abortions and stillbirths; study 3) in patients with NF1 in a nationwide population-based setting using large-scale record linkage techniques with national health outcome registers. Health-related outcomes will be documented in retrospective cohort studies of 2484 patients in the combined clinical and register-based NF1 cohort by linkage to nationwide health registries and compared with those in population comparisons

- to measure how patients with NF1 manage the transition from child- into adulthood in a similar approach by determining the following psychosocial and socioeconomic achievements or life goals based on information obtained from national population-based administrative registries: leaving home, cohabitation, and founding a family (study 4) as well as educational attainment (study 5)

- to thoroughly investigate the psychosocial burden (depression, anxiety, quality of life) (study 6) and impairment in cognitive functioning and need for professional support (study 7) among adults with NF1 in the clinical cohort using questionnaire-based patient-reported outcome measures (n=360) and neuro-psychological assessments performed by trained psychologists in a selected sub-sample (n=100)

2. KEYWORDS

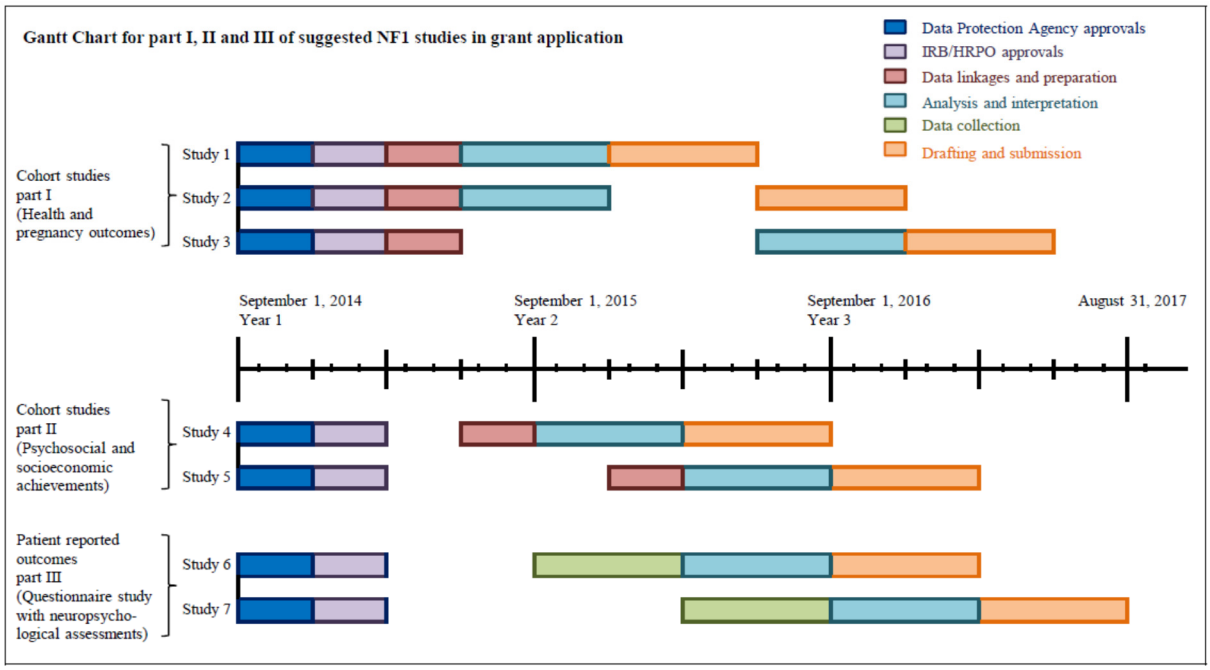
Neurofibromatosis type 1, population-based, nationwide, clinical epidemiology, somatic disease, mental disease, cohabitation, educational attainment, psychosocial burden, patient-reported outcomes, neuropsychological assessments

3. ACCOMPLISHMENTS

REFERRING TO THE FIRST ANNUAL REPORT

Major goals of project for year 1: According to the latest revised version of the SOW with first year estimated to start up September 1 2014 (inserted below; the contract ended up starting July 1), the major goals/tasks for the first year were to obtain all approvals before starting up the project (study 1-7) and to conduct data linkages and prepare for analyses (study 1-4).

Plan for next reporting period (year 2): Beside preparing the documents needed to be able to apply for HRPO approval to conduct studies 6 and 7, we stated in the first annual report that analyses would be conducted for studies 1, 2 and 4 and that a manuscript for study 1 would be drafted and submitted; i.e., that the postdoctoral fellow (Line Kenborg) and the scientific assistant (Karoline Doser) would start drafting manuscripts for study 2 and 4. Finally, we stated that we would develop a website that gives an overview of ongoing activities within the project and which disseminates the results of the research activities.



Accomplished under these goals

Approvals:

Within the first year, we accomplished to receive the initial approval from HRPO for all register-based studies 1-5, with the following limitation (see highlights below) (19 June 2015):

SUBJECT: *Initial Approval for the Protocol, "A Nationwide Population-Based Approach to Study Health-Related and Psychosocial Aspects of Neurofibromatosis Type 1," Submitted by Jeanette F. Winther, MD, Danish Cancer Society Research Center, Copenhagen, Denmark, Proposal Log Number NF130037, Award Number W81XWH-14-1-0054, HRPO Log Number A-18370.i*

1. *The subject protocol was approved by the Danish Cancer Society Research Center Institutional Review Board (IRB) on 23 October 2014. The US Army Medical Research and Materiel Command (USAMRMC), Office of Research Protections (ORP), Human Research Protection Office (HRPO) reviewed the protocol and found that it complies with applicable DOD, US Army, and USAMRMC human subjects protection requirements.*

2. The USAMRMC ORP HRPO approved this no greater than minimal risk study for the enrollment of approximately 2,500 subjects in the five registry studies. ***NOTE:*** *Separate HRPO approvals are required for the two additional studies embedded in this protocol, which include the questionnaire-based and patient reported outcome (study 6) and neuro-psychological assessments (study 7).*

Approval of studies 6 (questionnaire-study) and 7 (neuro-psychological assessments) was postponed because it required evaluation of all patient material, which were not prepared at that time, as development of patient material including questionnaires for this special patient group is a task within this research program.

Within this year (year 2), we have prepared all patient material for study 6 and 7 (See Appendix, pages 23-60). In June 30 2016, we applied for the permission from the Human Research Protection Office (HRPO) for final US approval to conduct these two studies (See Appendix pages 14-16 for cover letter to Derek T. Bowden, Human Subjects Protection Scientist, HRPO, ORP, US Army Medical Research & Material Command).

Data linkages:

Within the first year, we accomplished to 1) update the *clinical* NF1 cohort of patients affiliated to the two national Centers for Rare Diseases (CRD), 2) prepare a list of variables needed from the respective population-based registries to run the approved register-based studies (studies 1-5), and 3) send an request to the State Serum Institute and Statistics Denmark to obtain these data.

Within this year (year 2), we have accomplished:

- To select the population comparison subjects

- To send the cases (NF1 patients) and the population-based comparison cohort to the State Serum Institute and Statistics Denmark to obtain individual-level data on all outcomes data needed to analyze the register-based studies (studies 1-5).

- To have a final dataset ready for analyses for the register-based studies (studies 1-5). We have requested data from the following nationwide population-based registries:

    - The National Hospital Register (information on somatic disease)
    - The Danish Psychiatric Central Research Register (psychiatric disease)
    - The Medical Birth Register (birth variables including pregnancy outcomes)
    - The Danish National Prescription Registry (prescription drugs)
    - Statistics Denmark (leaving home, cohabitation, family, type and level of education)

Status on the respective studies:

List of suggested studies in this grant application (those highlighted are ongoing; remaining studies not started up yet)

Part I. Health and pregnancy outcomes in patients with NF1
Study 1: Somatic hospitalizations in patients with NF1 through all phases of life
Study 2: Psychiatric hospitalizations in patients with NF1 through all phases of life
Study 3: Adverse pregnancy outcomes in women with NF1

Part II. The transition from child- into adulthood for NF1 patients
Study 4: NF1 patients - Leaving home, cohabitation and founding a family
Study 5: Educational attainment among patients with NF1

Part III. Studies of the psychosocial burden and cognitive functioning and need for *professional support among adults with NF1*
Study 6: Psychosocial burden and need for professional support among adults with NF1
Study 7: Cognitive functioning and need for professional support among adults with NF1

Within this year (year 2), we have accomplished:

- To start up analyzing and drafting the manuscript for study 1 (still ongoing)

- To start up drafting the manuscript for study 5 (started up with study 5 instead of study 4, as originally stated in the section 'Plan for next reporting period' in the first annual report) (still ongoing)

- To prepare all patient documents needed for the studies 6 and 7 to be able to apply for HRPO approval

Study 1: Somatic hospitalizations in patients with NF1 through all phases of life

Aim:
The aim of this population-based study is to assess the risk of untoward somatic disorders in NF1 patients as measured by hospitalizations for diseases in all ages throughout life, compared to those in the general population. Dates and reasons for any hospitalization in these two cohorts between 1977 and today has been evaluated.

Methods:
The NF1 cohort includes 2517 NF1 patients. Further, 10 times as many population-based comparison subjects have been selected from the Central Population Register to measure rates of somatic morbidity in the background population.

By linking both study rosters to the National Hospital Register (NHR), which records information on nearly 99% of all admissions to non-psychiatric hospitals in Denmark, we have identified dates and reasons for any hospitalizations in both the patients and the comparisons. Each hospital admission initiates a record, which includes the personal identification number of the patient, dates of admission and discharge, a primary discharge diagnosis, and up till 20 supplementary diagnoses coded according to a Danish version of the International Classification of Diseases ICD-8 until 1993 and thereafter to ICD-10.

Discharge diagnoses have been grouped into 12 main diagnostic groups defined by the ICD-8 and 10-classification (infectious diseases, malignant neoplasms, benign neoplasms,

endocrine disorders, diseases of blood and blood-forming organs, diseases of nervous system and sense organs, diseases of circulatory system, diseases of respiratory system, diseases of urinary system and genital organs, diseases of digestive organs, diseases of skin and subcutaneous tissue, and diseases of bone, joints, and soft tissue) as well as several diagnostic sub-groups.

In a Cox proportional hazards model, we have estimated hospitalization rate ratios (HRRs) as a measure of the relative risk in the patient group compared to the population comparison group taking covariates into consideration and choosing age as the underlying time scale. Study subjects has been followed from birth or start of hospital register, which ever occurred latest, until age at first hospitalization using the date of admission, emigration, death, or the closing date of study, whichever occurred first. HRRs with corresponding 95% confidence intervals has been calculated for overall hospitalization and for hospitalization with a diagnosis within the main diagnostic groups (or selected sub-groups of specific interest), with population comparisons as referent. Excess absolute risks have been estimated as the differences in crude rates of hospitalization between patients and comparisons.

Preliminary results:
Comparing the observed and expected rates of hospitalization for overall somatic disease by attained age, preliminary data shows that NF1 patients are at an excess risk of being hospitalized in all age groups with the highest excess risk in the youngest and the oldest age groups. NF1 patients are at significantly increased risk of hospital admission for a somatic disease in nearly all 12 main diagnostic groups and in the vast majority of diagnostic sub-categories. As expected, NF1 patients who have been diagnosed with cancer had even higher risks.

A manuscript based on these findings is in preparation.

Study 5: Educational attainment among patients with NF1

A literature review has been conducted for this study and Karoline Doser has started drafting the introduction of this paper. Only sparse information is available about the academic performance of individuals with NF1 (Cutting & Levine, 2010; Gilboa, Rosenblum, Fattal-Valevski, Toledano-Alhadef, & Josman, 2014; Krab et al., 2008; Orraca-Castillo, Estévez-Pérez, & Reigosa-Crespo, 2014; Watt, Shores, & North, 2008). These studies have mainly investigated certain academic difficulties and disorders that might be a challenge during school-time for children with NF1 such as dyslexia and dyscalculia, attention deficits, and executive dysfunctioning. Only one study has reported on the impact of such difficulties on educational attainment reporting on repetitions of school grades (Coudé, Mignot, Lyonnet, & Munnich, 2006).

Previous studies have been limited by failure to be population-based or to be based on a large number of patients and most previous studies were based on self-reports (or rated by significant others) (Coudé et al., 2006; Cutting & Levine, 2010; Gilboa et al., 2014; Krab et al., 2008; Orraca-Castillo et al., 2014; Watt et al., 2008) (See Appendix, page 61 for overview of previous published studies within this research area with details on study design, methods and outcomes studied as well as the reference list.

No study has ever reported on the highest educational level attained in adults with NF1. Additionally, no information about potential delays in achieving certain academic levels is available. Using a population-based approach, the present study will contribute with unbiased information on educational performance in adults with NF1. Education is an important and challenging life goal for anyone - but even more significant for this patient group.

Studies 6 and 7: Psychosocial burden and need for professional support among adults with NF1 (study 6) and Cognitive functioning and need for professional support among adults with NF1 (study 7)

Research assistant Karoline Doser started September 1, 2015 on this project and has so far focused mainly on studies 6 (questionnaire-study) and 7 (neuro-psychological assessments).

During the review process of the original grant application to the US army, the reviewers had two major comments both related to study 7: 1) being lack of a control group and 2) the relatively narrow focus on Wechsler's IQ test (WAIS-IV) – a test chosen primarily due to budget constraints. Thus, to meet the requests from the reviewers and to improve study 7, we have made minor design revisions, specific revisions to the psychological assessment study 7, and minor revisions to the questionnaire in study 6. For further details, see Appendix, pages 17-22 for cover letter to Derek T. Bowden and the document entitled 'Life with Neurofibromatosis-NF1', pages 17-22.

Under the supervision of psychologist Pernille Envold Bidstrup and in collaboration with our clinical advisors and collaborators (Drs. John R Østergaard and Hanne Hove and our new collaborator clinical psychologist Jens Richardt Møllegaard Jepsen (see 'Other organizations involved as partner'), Karoline Doser has developed the following patient material for studies 6 and 7: invitation letter, patient information, informed consent form and for study 6 also a questionnaire. As soon as we have the approval from HRPO, data collection will start up.

Training and professional development:

Postdoctoral traineeship
One-on-one work: Line Kenborg has assisted Dr. Winther (her mentor) in the daily tasks related to the project.

Also in year two, Line Kenborg has attended the weekly seminars at the Danish Cancer Society Research Center and she has been organizing journal clubs and teaching younger colleagues and students at these meetings.

Line Kenborg has arranged at short research stay from 24 Oct-13 Nov 2016 at the Neurofibromatosis Institute, Los Angeles, USA and the Comprehensive Neurofibromatosis Clinic at Children´s Hospital, Los Angeles, USA with the overall purpose of clarifying further key elements of the natural history of NF1 and to discuss future collaborative studies with Dr. Vincent M. Riccardi and to visit Dr. Tena Rosser at her clinic in L.A. Children's Hospital (see Appendix, pages 62 for letter from Dr. Vincent M. Riccardi, Director, The Neurofibromatosis Institute).

Dissemination to communities of interest:
Nothing to report

Plan for the next reporting period (year 3):
During the next reporting period, analyses will be conducted for studies 2-5. Data collection will start up for studies 6 and 7 as soon as we have the HRPO approval. Manuscripts will be drafted and submitted as soon as analyses have been completed. See also section 5 below on changes/problems.

Information on this research program can be found on the website of the Danish Cancer Society Research Center on the following link:

https://www.cancer.dk/research/survivorship/childhoodcancersurvivors/svpcssneurofibromatosis/

A website for this specific research program will be developed that gives an overview of all ongoing activities within the program and which disseminates the results of the research activities.

4. IMPACT
Nothing to report

5. CHANGES/PROBLEMS

Changes:

As mention above in ACCOMPLISHMENTS in the paragraph 'Status on the respective studies', study 6 and 7, minor design revisions, specific revisions to the psychological assessment study 7, and minor revisions to the questionnaire in study 6 have been made and is now under review by HRPO.

Problems:

We are a little behind schedule. Postdoc Line Kenborg, who will be the first author for the register-based studies 1-3 is on maternity leave. Further, we await the permission from HRPO to be able to send out questionnaires (study 6) and start up patient interviews (study 7). Karoline Doser will be the first author of these two studies as well as the first author of the register-based studies 4 and 5.

I have, however, a large team of senior researchers and postdocs on this project, so other researchers within the team might take over the responsibility for writing up some of the papers to meet the deadlines.

At the moment, I consider to apply for a 1 year no-cost extension of the project. Whether this will be needed depend on when I receive the HRPO approval for the studies 6 and 7, as data collection for these two studies is time consuming.

6. PRODUCTS

- A full dataset on somatic disease in NF1 patients and in 10 times as many population-based comparison subjects based on discharge diagnoses obtained from the National Hospital Register.
- Patient information in Danish (and English) (see Appendix, pages 23-60)
- A questionnaire consisting of a standardized part (Pediatric Quality of Life Inventory-NF1 Module (PedsQL)) translated into Danish and a part on demographics, socioeconomic status, and need for professional support developed within our research group (See Appendix, pages 32-50)

7. PARTICIPANTS AND OTHER COLLABORATING ORGANIZATIONS

Individuals who have worked on the project

Name:	Jeanette Falck Winther
Project Role:	PI
Researcher Identifier (e.g. ORCID ID):	ORCID ID: 0000-0002-3440-5108
Nearest person month worked:	1
Contribution to Project:	Dr. Winther has been overall responsible for the project and for the overall coordination of the project including contact with internal and external collaborators on the project and all contact with the US Army
Funding Support:	See section 'Change in the active other support' below

Name:	Line Kenborg
Project Role:	Postdoctoral fellow
Researcher Identifier (e.g. ORCID ID):	-
Nearest person month worked:	4,5 months
Contribution to Project:	Line Kenborg has assisted Dr. Winther by being responsible for the daily tasks related to the project and she has drafted the paper on

	somatic disease in NF1 patients (still ongoing) until her maternity leave (mid-December till September 2016)
Funding Support:	-

Name:	Karoline Doser
Project Role:	Research assistant
Researcher Identifier (e.g. ORCID ID):	ORCID ID 0000-0002-2746-3326
Nearest person month worked:	10
Contribution to Project:	Karoline has developed the patient material for the studies 6-7, set up a questionnaire consisting of a set of standardized measures as well as several self-developed questions on demographics and socioeconomic status, translated the Pediatric Quality of Life Inventory – NF1 Module (PedsQL) based on the standardized linguistic validation procedure, made a review of the literature for study 5 on educational attainment among NF1 patients and has started up drafting the manuscript.
Funding Support:	Karoline Doser has applied the Innovation Fund Denmark and the Lundbeck Foundation for further funding including her salary for one year (to combine with the two years of salary from the US Army) with the overall purpose of being enrolled at the University of Copenhagen as a PhD student

Name:	Anne Katrine Duun-Henriksen
Project Role:	Statistician
Researcher Identifier (e.g. ORCID ID):	-
Nearest person month worked:	6 months
Contribution to Project:	Anne Kathrine Dunn-Henriksen has prepared data for analyses and has analyzed data on somatic disease in NF1 patients

Funding Support:	-

Name:	Doris Shannon Rohrer
Project Role:	Project assistant
Researcher Identifier (e.g. ORCID ID):	-
Nearest person month worked:	4,5 months (working hours: 20 hours per week)
Contribution to Project:	Doris Rohrer has assisted Dr. Winther and her team in the daily tasks related to the project
Funding Support:	-

Change in the active other support of PI/key personnel:

Jeanette Falck Winther

The following grant has now closed:

Title: Adult Life after Childhood Cancer in Scandinavia (ALiCCS)

*Time commitment***:** 50%

Supporting agency: The Danish Council for Strategic Research (grant no. 09-066899)

Address of the funding agency's Grant Officer: Ministry of Science, Innovation and Higher Education
Slotsholmsgade 10, 1216 Copenhagen K, Denmark. No specific grant officer.

Performance period: January 2010 to December 2014

Level of funding: 90%, *Role*: Co-investigator

Goals and aims of the study: To study late effects after treatment for cancer in a combined Nordic cohort of childhood cancer survivors. Detailed knowledge on late effects according to type of childhood cancer will strengthen the possibilities of planning preventive initiatives. The overall goal is to prevent and minimize late effect among childhood cancer survivors.

The following grants are new active grants:

1)
Title: Adult Life after Childhood Cancer in Scandinavia (ALiCCS): Socioeconomic consequences of long-term survival

Time commitment: 16,7%

Supporting agency: NordForsk

Address of the funding agencies Grant Officer: NordForsk, Stensberggata 25, NO-0170 Oslo; Grant officer: Senior adviser Maria Nilsson, PhD

Performance period: January 2016 - December 2018

Level of funding:100%; *Role:* PI

Goals and aims of the study: To evaluate the socioeconomic consequences of surviving childhood cancer in a Nordic setting.

2)
Title: Adult Life after Childhood Cancer in Scandinavia (ALiCCS) – in depth evaluation of late effects including detailed treatment information and organ radiation dosimetry

Time commitment: 0% (funds to pay radiophysicists at Aarhus University Hospital, Skejby and at M.D. Anderson Cancer Center in Houston, Texas for conducting organ radiation dosimetry)

Supporting agency: The Danish Childhood Cancer Foundation

Address of the funding agencies Grant Officer: The Danish Childhood Cancer Foundation, Dampfærgevej 22, P.B. 847, DK-2100 Copenhagen, Denmark - no specific grant officer

Performance period: November 2015 - December 2018

Level of funding: 100 %; *Role:* PI

Goals and aims of the study: To evaluate organ radiation dosimetry (scattered radiation to a variety of organs from the tumor field in children treated for cancer) to be used for several case-cohort studies designed to investigate associations between specific elements of treatment regimens and risk of late effects conducted within the original ALiCCS research program supported by the Danish Council for Strategic Research.

3)
Furthermore, I have received a small donation from the staff of a Danish bank (Jyske Bank/BFR-Kredit) to support the ALiCCS research program.

Other organizations involved as partners:
Clinical psychologist Jens Richardt Møllegaard Jepsen, M.Sc., Psychiatric Center Copenhagen, Copenhagen University Hospital Bispebjerg in Denmark is a new collaborator coming into our team. Sharing his experience and expertise with us, Jens R. M. Jepsen has generously offered as an unpaid collaborator to be in charge of training psychology students for conducting the neuropsychological assessment. Using this approach rather than using independent psychology consultants allows us to re-allocate financial resources to address the limitations of our study 7 raised by the reviewers. Jens Richardt Møllegaard Jepsen will contribute to study 6 and 7.

Dr. John M Mulvihill, MD, Professor of Pediatrics, The University of Oklahoma, Health Sciences Center, has been invited into our team as an unpaid collaborator. Dr. Mulvihill is a clinical geneticist with great expertise within this research field. Having him as an adviser and collaborator will be a great contribution to the clinical aspects and the science of this research program.

8. SPECIAL REPORTING REQUIREMENTS
Nothing to report

9. APPENDICES

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UNDER PROTECTION OF
HER MAJESTY THE QUEEN

June 30 2016

Derek T. Bowden
Human Subjects Protection Scientist
HRPO, ORP
US Army Medical Research & Material Command

Protocol: "A Nationwide Population-Based Approach to Study Health-Related and Psychosocial Aspects of Neurofibromatosis Type 1", Proposal Number NF130037, Award Number W81XWH-14-1-0054, HRPO Log Number A-18370

Dear Derek T. Bowden,

In 2014, we have obtained permission from the US Human Research Protection Office (HRPO) to conduct the sub-studies 1-5 of the study research program 'A nationwide population-based approach to study health-related and psychosocial aspects of neurofibromatosis type 1' including a total of 7 sub-studies funded for three years by the US Army.

Approval of sub-studies 6 (questionnaire-study) and 7 (neuro-psychological assessments) was postponed because it required evaluation of all patient material, which were not prepared at that time - as development of patient material including questionnaires for this special patient group is a task within this research program.

We have now prepared all patient materials for study 6 and 7. Furthermore, we have made minor design revisions, which is explained in more details below with the overall aim of meeting the requests from the reviewers of our original grant application and to improve our study.

We hereby apply for the permission from the Human Research Protection Office (HRPO) for final US approval to conduct these two studies.

Minor design revisions
During the review process of the original grant application to the US army, the reviewers had two major comments both related to study 7: 1) being lack of a control group and 2) the relatively narrow focus on Wechsler's IQ test (WAIS-IV) – a test chosen primarily due to budget constraints.

Clinical psychologist Jens Richardt Møllegaard Jepsen, M.Sc., Psychiatric Center Copenhagen, Copenhagen University Hospital Bispebjerg in Denmark is a new collaborator coming

into our team. Jens R. M. Jepsen has generously offered as an unpaid collaborator to be in charge of training psychology students for conducting the neuropsychological assessment. Using this approach rather than using independent psychology consultants allows us to re-allocate financial resources to address these two limitations of our study 7 raised by the re-viewers. Thus, we have made some revisions as described below.

Revisions to the psychological assessment study 7:

- A new aim of comparing cognitive functioning in NF1 patients with healthy controls has been added
- Psychological assessment of this control group (n=50 adults) has been added
- Psychological assessments will be conducted by trained psychology students instead of psychologist consultants
- The IQ-testing using WAIS-IV has been reduced from a full assessment (1.5-2 hours) to the abbreviated four-subtest form (according to the Wechsler Abbreviated Scale of Intelligence - WASI II); i.e., the minimum of sub-testing needed still allowing overall IQ evaluation (30 minutes)
- Scales on social recognition (SRS-II 10-15 minutes) has been added to the neuropsychological assessment interview
- The assessment of executive functioning and attention by using 7 subtests of the Cambridge Neuropsychological Test Automated Battery (CANTAB) has been added (1 hour)
- A paper based test for verbal memory has been added (15 minutes)
- Power calculations were performed on the new domains and showed a power of 99% for a sample size of 100 patients and 50 controls (see attached document on power calculation)

To improve study 6, we have also made some minor revisions.

Minor revisions to the questionnaire in study 6:

- The Major Depression Inventory (MDI) and the Symptom Checklist-90 Revised (SCL-92-R) has been replaced by the Patient Health Questionnaire (PHQ-9) and the Generalized Anxiety Disorder Scale (GAD-7) as they allow Diagnostic and Statistical Manual (DSM) diagnostic criteria (5 minutes each)
- A scale measuring attention deficit hyperactivity disorder (ADHD); i.e., the Autism Spectrum Rating Scale (ASRS-II) for adults (18 items, 10 minutes) has been added
- A scale measuring fatigue; i.e., the Multidimensional Fatigue Inventory (MFI) 20 (12 items, 5 minutes) has been added

As defined by the "Danish Act on Research Ethics Review of Health Research Projects" Section 2, the project does not constitute a health research project, but is considered a register research project as well as interview- and questionnaire-based study. Thus, the project can be initiated without approval from The Committees on Health Research Ethics for the Capital Region of Denmark (letter attached). The study has been approved by the Danish Data Protection Agency (permission attached).

Finally, I would like to stress that all seven studies will not have greater than minimal risk - if any at all - to the patients, as we do not include any invasive procedures.

On behalf of my research team,

Yours sincerely,

Dr. Winther

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List of attached documents:

- Original documents (study protocol, technical abstract, lay abstract, statement of work)
- Permissions (Danish Data Protection Agency, letter from the Committees on Health Research Ethics for the Capital Region of Denmark, local IRB approval of study 1-5, US approval of study 1-5)
- Revised protocol description of study 6 and 7 including table of measurements and tests
- Patient material for study 6 in Danish (invitation letter, patient information, questionnaire, informed consent)
- Patient material for study 7 in Danish (invitation letter, patient information, informed consent)
- Power calculation illustrating the power of the sample size for study 7
- Approval from the local IRB
- Danish documents sent to and approved by the local IRB

Life with Neurofibrtomatosis-NF1

Psychosocial burden and need for professional support among adults with NF1 (study 6 in application)

Aim In a questionnaire-based study among 360 adults with NF1, we will examine 1) the prevalence of patients with moderate and high self-reported psychosocial burden, 2) disease-related and demographic factors associated with the psychosocial burden as well as 3) need for professional support related to the psychosocial burden. The primary outcome will be depression and secondary outcomes include: anxiety, need for professional support related to psychosocial burden, and quality of life.

Material and Methods *Design: The p*sychosocial burden will be examined in a cross-sectional study among all Danish NF patients age 15 or above (n=450) registered in the population-based clinical cohort the Danish Centers for Rare Disease using questionnaire-based patient-reported outcomes. We expect a response rate of 80% resulting in a total of 360 participants.

Procedure for data collection: An important challenge in collecting questionnaire data in this patient population is that up to 75% of the patients have impaired cognitive functioning [1]. This will make it difficult for the participant to answer a questionnaire and could potentially influence the response rate or the number of missing items on the returned questionnaire. We will address this issue when constructing the questionnaire (using few and short measures) and by making it possible to be assisted by a relative or by being interviewed over the phone. In the invitation letter it will be stated that such a telephone-interview can be requested. Patients registered in the clinical NF1 cohort will receive a letter of invitation including their treating physician's permission to contact them, a paper-based questionnaire, an informed consent form, as well as a pre-paid return envelope. If the questionnaire is not returned within 21 days, a reminder letter will be sent. If the questionnaire is still not returned after another 14 days, a telephone reminder will be made. Here, the participant will also have the option of a telephone interview.

The *primary outcome* depression will be measured using the Danish version of the Patient Health Questionnaire depression scale (PHQ-9) developed by Spitzer et al. according to the DSM-IV criteria [2]. *Secondary outcomes* will include anxiety measured with the Generalized Anxiety Disorder (GAD-7) [3], which is validated in Danish, and quality of life measured using the Pediatric Quality of Life Inventory™ (PedsQL). The PedsQL was developed and validated in English specifically for NF patients including the following dimensions: physical functioning, emotional functioning, social functioning, communication, worry, perceived physical appearance, pain and hurt, paresthesias, skin irritation, sensation, movement and balance, daily activities, fatigue, treatment anxiety, and sexual functioning [4]. We will use standard forward-backward translation procedures to translate the PedsQL from English to Danish [5]. Data will also be collected on the cognitive functioning dimension from the PedsQL.

To effectively identify symptoms, behaviors and associated features of ADHD, the Danish version of the Adult ADHD Self-Report-Scale (ASRS II) shall be used. This symptom checklist consists of eighteen DSM-IV-TR criteria rated based on a Likert-scale ranging from 1 (never) to 5 (very often) [6]. Six of the eighteen questions were found to be the most predictive of symptoms consistent with ADHD.

Other measures included in the questionnaire The questionnaire will also measure use of professional support in the health care system and need and wish for such support using individual items developed

for this study and tested in 10 pilot interviews. Disease severity will be measured using a dichotomized Riccardi scale (low grade 1-2, high grade 3-4) [7]. Here the patient is asked to rate the impact of their NF1 manifestations on a scale from 1-4. Patients with grade 3-4 have at least one of the following disease-related symptoms: pseudarthrosis, hypertension/cardiac defects, epilectic seizures, precocious or delayed onset of puberty, brain tumor, pheochromocytma, cancer or disfiguring neurofibromas. The Ablon scale [8] will be used to evaluate the visibility of the disease. The ratings are based on appearance of the person fully dressed and how readily physical symptoms could be perceived in impersonal interaction thus grouping patients into grade 1 (mild), grade 2 (moderate) and grade 3 (severe). We develop self-reported versions of the Riccardi as well as the Ablon scales based on the Danish proxy versions used by physicians. Information on family structure (having a partner on a yes/no level and number of children, if any) will also be collected.

Statistical analyses Using the questionnaire-based data we will examine a) the prevalence of patients with moderate and high psychosocial symptom burden (depression, anxiety and symptoms reported in the PedsQL), associations between b) disease-related (disease severity and treatment) and socio-demographic factors (partner and children) and psychosocial burden (depression, anxiety, quality of life) as well as between c) psychosocial burden (depression, anxiety, quality of life) and need for professional support. Analyses will be conducted using both dichotomized versions and continuous versions of the psychosocial measurements applying logistic and linear regression models, respectively. When available, mean outcome scores will be compared to Danish or international norm scores. Analyses will when relevant be adjusted for confounders including demographic factors (age, gender, partner). All tests will be two-tailed, significant at the 5 % level and estimates will be accompanied by 95% confidence intervals. The generalizability of the questionnaire data will be examined by evaluating if health or socio-economic factors are differently distributed in the questionnaire population compared to the register-based NF1 cohort of all patients hospitalized for NF1 in Denmark.

Questionnaire	Test	Outcome
	Demographics	-
	Pediatric Quality of Life Inventory (Peds QL)- NF1 Module	Quality of life in NF1 patients
	Riccardi scale (adapted to a Danish self-report version)	Severity of NF1
	Ablon scale (adapted to a Danish self-report version)	Visibility of NF1
	Adult ADHD Self-Report Scale (ASRS II)	Attention deficit
	Generalized Anxiety Disorder (GAD7)	Anxiety
	Patient Health Questionnaire depression scale (PHQ9)	Depression
	Multidimensional Fatigue Inventory (MFI20)	Fatigue

Cognitive functioning and need for professional support among adults with NF1 (study 7 in application)

Aim In this study, cognitive functioning will be examined in two sub-populations: a cross-sectional study among all adults with NF1 from the clinical NF1 cohort using questionnaire-based patient-reported outcomes and neuropsychological assessment in a selected sub-group of 100 patients in comparison with 50 matched NF1-free persons. We will examine 1) the prevalence of impaired cognitive functioning in NF1 persons compared to NF1-free persons, 2) disease-related and demographic factors associated with cognitive functioning and 3) need for professional support related to cognitive functioning. The primary outcome will be the overall impairment in cognitive functioning (IQ) and the secondary outcome the need for professional support related to cognitive functioning.

Material and Methods *Data collection:* Cognitive functioning will be examined in two sub-populations: the cross-sectional study described in study 2 among all adults with NF1 (approximately 360 participants) from the population-based clinical NF1 cohort using questionnaire-based patient-reported outcomes and in a selected sub-group of 100 patients and 50 NF1-free persons using questionnaire-based patient-reported outcomes as well as neuropsychological assessment.
Questionnaire based data collection: Information on cognitive functioning (PedsQL) will be obtained from the prior collection of data in the questionnaire-based study 6 including approximately 360 participants.

Data collection for the cognitive functioning: A sub-group of 100 patients from the questionnaire study will participate in the neuropsychological assessment and will be compared with neuropsychological assessments and questionnaire data in 50 randomly-selected matched NF1-free persons.

When invited to the questionnaire study, participants are asked to participate in the cognitive test study. Upon written informed consent, the participant will be contacted by phone to set up an assessment appointment. The assessments will take place at home or at the closest rare disease clinic, depending on the patient's choice. The assessments will be performed by one of six psychologists with special training in neuropsychological testing and will last 2 to 2 ½ hours. After the assessment, the psychologist will score the test, which will take approximately ½ hour. A detailed guide for the test procedure will be developed to supplement the test manuals for the individual test in our test-battery. To get familiar with the standardized test-material and the procedure, the psychologists will participate in a 3 day training course. During 5 pilot tests, the psychologists will observe each other and give feed-back. The participants, patients as well as healthy controls, will be offered 400 kr. (USD 70) for study participation.
Among the NF1 patients, we expect a 50% response rate. To reach a sample of 100 NF1 patients, 200 NF1 patients will be invited. In the sampling, we will aim to sample 100 NF1 patients that represents the NF1 population on age and gender. When sampling the NF1-free persons we expect a 40 % response rate, thus 125 persons will be invited.

Questionnaire-based patient-reported cognitive functioning Cognitive functioning will be measured using the sub-scale (5 items) from the PedsQL for NF1 patients, which taps into concentration and memory [4]. We will use standard forward-backward translation procedures to translate the PedsQL from English to Danish [5]. To identify social impairment associated with autism spectrum disorder the Social Responsiveness-scale (SRS-2) will be used [9]. Additionally, the (BRIEF) shall be used to obtain information and executive functioning [10]

Assessment instrument The neuropsychological assessment will enable a thoroughly and theoretically appropriate evaluation of the cognitive functioning by using four-subtest abbreviated version of the Wechsler Adult Intelligence Scale (WAIS-IV) [11] which has been validated in Danish. The following dimensions will be evaluated: estimated IQ, measure of crystallized abilities, measure of nonverbal fluid abilities and visuomotor/coordination skills. The Cambridge Neuropsychological Test Automated Battery (CANTAB) [12] will assess executive functioning (planning and abstract concept formation), and attention (sustained and switching). Memory will be assessed by using Rey's complex figure test (RCFT) [13].
Statistical analysis Using the questionnaire-based data we will examine a) the prevalence of patients with impaired cognitive functioning (PedsQL) in NF1 persons compared with NF1-free persons, and associations between b) disease-related (disease severity and treatment) and socio-demographic factors and cognitive functioning (PedsQL) as well as between c) cognitive functioning (PedsQL) and need for professional support. Similar analyses will be conducted on data based on neuropsychological assessment to examine associations between a) the prevalence of patients with impaired cognitive functioning (WAIS-IV and CANTAB) in NF1 persons compared with NF1-free persons and b) disease-related and socio-demographic factors and cognitive functioning (WAIS-IV and CANTAB) as well as

between cognitive functioning (WAIS-IV and CANTAB) and need for professional support. When available, mean outcome scores will be compared to Danish or international norm scores. Finally, in order to calibrate the cognitive functioning data using PedsQL, correlation coefficients will be used to estimate differences between cognitive functioning measured using PedsQL and selected WAIS-IV dimensions. Analyses will be conducted using both dichotomized versions and continuous versions of the cognitive functioning measurements applying logistic regression models and linear regression models, respectively. Analyses will when relevant be adjusted for confounders including demographic factors (age, gender, partner). All tests will be two-tailed, significant at the 5% level and estimates will be accompanied by 95% confidence intervals. The generalizability of the questionnaire data will be examined by evaluating if health or socio-economic factors are differently distributed in the questionnaire population compared to the total rare disease population in the register-based cohort of patients hospitalized for or with NF1 in Denmark.

Implications These two studies of patient-reported outcomes and objective neuropsychological assessment will be the largest to date and with minimal selection bias. They will contribute with detailed information on the psychosocial burden measured as depression, anxiety, and quality of life and cognitive function impairments in adult patients and their need for professional support never previously elucidated.

Perspectives and ultimate goals

No previous study has been able to measure how NF1 patients manage the transition between child- and adulthood by determining psychosocial and socioeconomic achievements or life goals and only few studies with low number of patients have elucidated the psychosocial burden and impairment in cognitive functioning in patients in different stages of adulthood. The clinical information provided by the suggested studies will fill these gaps of knowledge and improve our understanding of the implications this complicated disease may have on life – information that is highly requested by the patients and their families, but also by the clinicians advising these patients. The results of the suggested studies of social aspects of life in this patient group in combination with potential predictors of well-being and functioning from the questionnaire studies can be used for developing a systematic plan for longitudinal screening and evidence-based guidelines for surveillance. The ultimate goals are to contribute to the development of targeted intervention strategies to improve the basis for patient counseling and to optimize follow-up procedures, leading to high quality of care and sufficient support to NF1 patients.

Ethical and legal aspects

Permission has been obtained from the Danish Data Protection Agency (July 2014), the local Institutional Review Board (IRB) (October 2014 and November 2015) and the HRPO (June 2015) (study 4; studies 6 and 7 still needs to be approved). As defined by the "*Danish Act on Research Ethics Review of Health Research Projects*", the project does not constitute a health research project, but is considered a register research project as well as interview- and questionnaire-based study. Thus, the project can be initiated without approval from The Committees on Health Research Ethics for the Capital Region of Denmark.

Neuropsychological assessment	Test	Subtest	Outcome
	Social Responsiveness Scale (SRS 2)		Social impairment / autism spectrum disorder
	Wechsler Adult Intelligence Scale (WAIS IV)	Vocabulary	Estimate of general cognitive ability
		Similarities	
		Block design	Measure of crystallized abilities
		Matrix reasoning	Measure of nonverbal fluid abilities and visuomotor/coordination skills
	Cambridge Neuropsychological Test Automated Battery (CANTAB)	Motor control task (MOT)	Introduction
		Attention switching task (AST)	Executive function
		One-touch Stockings of Cambridge (OTS)	
		Spatial Span (SSP)	
		Spatial working memory (SWM)	
		Rapid Visual Information Processing (RVP)	Attention
		Reaction time (RTI)	Attention
	Paper based memory test	e.g. Rey's complex figure test (RCFT)	Memory

References

1. Krab, LC, Aarsen, FK, de Goede-Bolder, A, Catsman-Berrevoets, CE, Arts, WF, Moll, HA, Elgersma, Y. Impact of neurofibromatosis type 1 on school performance. J. Child Neurol. 2008;23(9):1002-1010.
2. Kroenke, K., Spitzer, R., Williams, W. The PHQ-9: Validity of a brief depression severity measure. JGIM. 2001;16: 606-616.
3. Spitzer, RL, Kroenke, K, Williams, JBW, Lowe B. A brief measure for assessing generalized anxiety disorder. Arch Inern Med. 2006;166:1092-1097.
4. Nutakki, K, Hingtgen, CM, Monahan, P, Varni, JW, Swigonski, NL. Development of the adult PedsQL neurofibromatosis type 1 module: initial feasibility, reliability and validity. Health Qual.Life Outcomes. 2013;1121.
5. Beaton, DE, Bombardier, C, Guillemin, F, Ferraz, MB. Guidelines for the process of cross-cultural adaptation of self-report measures. Spine (Phila Pa 1976.). 2000;25(24):3186-3191.
6. Kessler, RC, Adler, L, Ames, M, Demler, O, Faraone, S, Hiripi, E, Howes, MJ, Jin, R., Secnik, K, Spencer, T, Ustun, TB, Walters, EE. The World Health Organization Adult ADHD Self-Report Scale (ASRS). Psychological Medicine, 2005; 35(2), 245-256.
7. Riccardi, VM. Von Recklinghausen neurofibromatosis. N.Engl J.Med. 1981;305(27):1617-1627
8. Ablon, J. Gender response to neurofibromatosis 1. Soc Sci Med. 1996; 42(1), 99–109.
9. Constantino, JN, & Gruber, CP. Social Responsiveness Scale, Second Edition. Los Angeles, CA: Case Western Psychological Services. 2012.
10. Roth RM, Isquith PK, Gioia GA. Behavioral Rating Inventory of Executive Function—Adult version. Psychological Assessment Resources, Inc., Lutz, FL 2005
11. Wechsler D. Wechsler Adult Intelligence Scale–Fourth Edition. Pearson; San Antonio, TX: 2008.

12. Sahakian BJ, Morris RG, Evenden JL, Heald A, Levy R, Philpot M, Robbins TW. A Comparative Study ofVisuospatial Memory and Learning in Alzheimer-Type Dementia and Parkinson's Disease. Brain. 1988;111(3):695–718.
13. Rey A. L'examen psychologique dans les cas d'encephalopathie traumatique. Archives de Psychologie, 1941. 28, 286–340

life with NF1

Date

Name and adress

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UNDER PROTEKTION AF
HENDES MAJESTÆT DRONNINGEN

Invitation to participate in the research project *Life with neurofibromatosis NF1*

Dear XX,

We kindly invite you to participate in the questionnaire study *Life with Neurofibromatosis* as we would like to gather information about the daily life of adults with NF1. We hope this study will bring knowledge to the health care system and the municipalities that can contribute to improving the support offered to adults with NF1.

What does it imply to participate in the study?
Please, read "Information to participants", and fill in the questionnaire and the informed consent form and return these two documents to us in the enclosed pre-paid envelope **before xx.xx.2016.**

Do you have questions?
Please, contact project assistant Doris Shannon Rohrer, by phone 3525 7650 (Monday to Wednesday 11:00 AM-2:00 PM) or by e-mail: dsr@cancer.dk

Thank you in advance for your help.

Yours sincerely,

Karoline Doser, PhD student
Pernille Bidstrup, senior researcher, psychologist, PhD
Jeanette Winther, principal investigator, Consultant, MD, DMSc
Danish Cancer Society Research Center

The study is performed in close collaboration with:

Center for Rare Disease, Rigshospitalet, Copenhagen
Hanne Hove, Consultant, MD

Center for Rare Disease, Aarhus University hospital
John Rosendahl Østergaard
Professor, Consultant, MD

NF Organization
Lene Lind, Chairman
www.nfdanmark.dk

Information to participants

livet med NF1

Information to participants on the research project *Life with neurofibromatosis – NF1*

Questionnaire


Jeannette


Doris


Pernille


Karoline

life with NF1

There is a need for knowledge in the health care system and municipalities on how to support adults with NF1.

With the study "Life with neurofibromatosis – NF1" we wish to gather and share knowledge about the everyday life of adults with NF1.

We are contacting you to ask if you are interested in participating in this study. Before you make a decision you can read about the study and why we are conducting it on the following pages.

Investigator and collaborators

Jeanette Falck Winther, principal investigator, Consultant, MD, DMSc

Doris Shannon Rohrer
Project assistant

Pernille Bidstrup
Senior researcher, psychologist, PhD,

Karoline Doser
PhD student

Danish Cancer Society
Research Center

Why this NF1 study?
NF1 is a disease that can have many different health consequences. However, we still know very little about the everyday life of adults with NF1. When you have a rare disease like NF1 you often meet people who do not know anything about the disease, and you often need to explain how you are doing – also to health professionals, the municipality and at work.

We kindly ask for your help to investigate how it is to live with NF1. Your answers can help us to document the physical, psychological and social aspects of NF1 and what type of needs for support a person with NF1 might have.

Participation in the study
If you are interested in participating, we kindly ask you to fill in the questionnaire and the informed consent form and return the two documents to us in the pre-paid envelope.

The questions in the questionnaire concern physical and psychological challenges, quality of life and everyday life with your family and at work. There are also some questions related to your memory and concentration.

Help with the questionnaire
Some questions may be difficult to answer. You are welcome to ask someone to help you answer the questionnaire, but it is important that it is *your* answers you enter. You may also call our project assistant Doris Rohrer (phone 3525 7650) so you can go through the questionnaire together on the phone.

Who can participate?
Adults above the age of 18 diagnosed with NF1 can participate. We hope that 400 persons are willing to participate.

Your answers are important to us
NF1 is a rare disease so all answers are very important as they add value to the project. Even if you do not have any symptoms, your answers are still important to us. The more answers we get the more likely it is that the results can be used to improve the support to persons with NF1 both in Denmark and in other countries.

What do you get out of the study?
Unfortunately, we are unable to offer a honorarium for your participation. If you are interested, we will send you a description of the results when the study has been completed. We will ask about that on the consent form.

Voluntary participation
Participation in the study is voluntary. You can withdraw from the study at any time without giving a reason or explanation. Your ongoing treatment will not be affected whether you choose to participate or not.

All information will be treated with full confidentiality, and all staff working on the project has a duty of confidentiality. Information about your health as well as other confidential information may be forwarded to persons who administer a compulsory quality control of the research study. The project is approved by the Danish Data Protection Agency (jr.nr: 2014-41-2935), which means it fulfills all requirements given by the Danish State concerning data protection.

Research on concentration and memory
We would also like to invite some of you to participate in an interview on concentration, memory and intelligence. The interview can take place in your home or at the Center for Rare Disease in Aarhus or Copenhagen. Together we will perform some small tasks, which takes around 2 hours. We will contact some of you to explain more about the interview and arrange a time to meet.

We hope that this part of the research project will give us more knowledge about the challenges that adults with NF1 may face with memory and concentration and how this affects everyday life. This knowledge can be used by the healthcare system and the municipalities to support adults with NF1, e.g. in getting an education or finding or keeping a job.

Who is behind the study?

Jeanette Falck Winther,
Consultant,MD, DMSc
Principal investigator and coordinator
Danish Cancer Society Research Center

Collaborators:

Danish Cancer Society Research Center

Karoline Doser
PhD student

Pernille Bidstrup
Senior researcher, psychologist, PhD,

Susanne Dalton
Senior researcher, MD, PhD

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Professor, Consultant, MD

NF Organization
Lene Lind, Chairman
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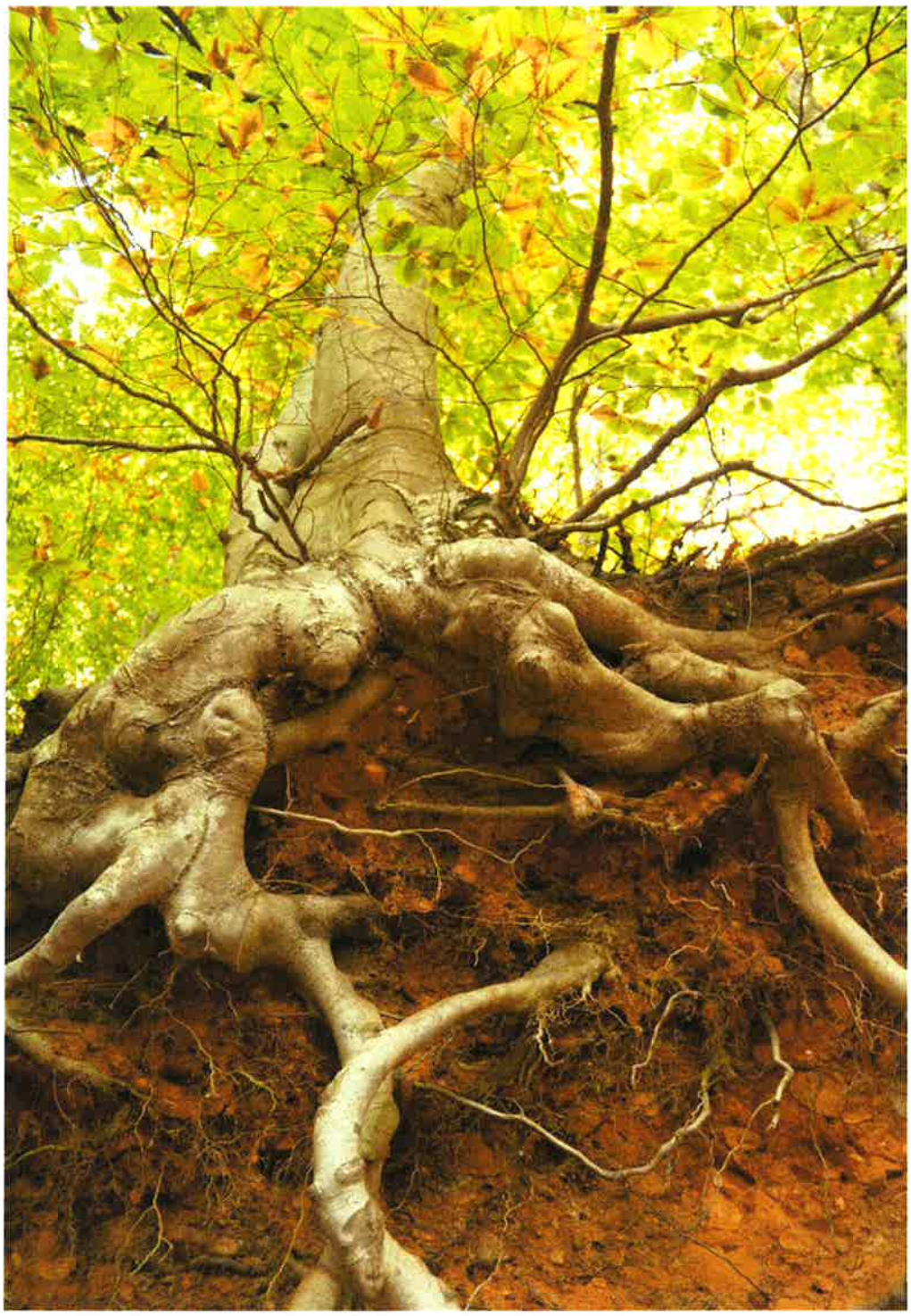
Research Unit, Psychiatric Center Glostrup & Children and Youth Psychiatric Center, Capital Region of Denmark

Jens Richardt Møllegaard Jepsen
Senior researcher, psychologist, PhD



Contact

If you have any questions, please contact:

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U.S. Army Medical Research and Materiel Command
Congressionally Directed Medical Research Programs
2013 Neurofibromatosis Research Program

Questionnaire

life with NF1

study-ID number: | | | |

How to complete the questionnaire

It takes about 30 minutes to answer all the questions . It is important that you try to answer all the questions as the quality of the study improves the more questions you answer. The information in the questionaire will be treated strictly confidentially. No information will be published which could be associated with you personally.

As the questionnaire is processed electronically, it will be a great help if you:

- Fill out the questionnaire using a blue or black pen
- Read the instructions and all possible answers to each question carefully before answering
- Use clear X's inside the boxes ☒
- In case you answer incorrectly, strike out the box with the wrong X completely ■. You can then put the X in the right box.
- Write numbers as follows

1	2	3	4	5	6	7	8	9	0

If you have difficulties filling in the form or any questions in the questionnaire, please feel free to call or send an e-mail to:

Doris Shannon Rohrer
Projectassistant
Survivorship unit
Danish Cancer Society Research Center
Strandboulevarden 49
2100 København Ø

Tlf. 3525 7500
E-mail: dsr@cancer.dk

Please start here

Date of completion of the form. If you use several days write the day you beginn: ..... Date | | Month | | Year 2 0 | |

1. When were you born? ..... Date | | Month | | Year 1 9 | |

2. How tall are you? ..... | | | cm

3. What is your weight? ..... | | | kg

Doris Shannon Rohrer, Livet efter kræft, Kræftens Bekæmpelses center for kræft forskning– Telefon: 3525 7500

Family

4. Do you have a partner (spouse or boy-/girlfriend)? ..... Yes ☐ No ☐

If you do not have a partner right now:

Do you wish you had a partner? ..... Yes ☐ No ☐

5. How many children do you have? ..... ☐☐ children

If you do not have children:

6. Do you want to have children? (Please tick only one box)

No, I do not want children because I am concerned that they will inherit NF1 ☐

No, I do not want to have children for reasons other than NF1..... ☐

Yes, I want children, but not until I find a partner..... ..... ☐

Yes, I would like to have children with my partner now, but we are unable to have children ..... ☐

I do not know yet whether I want to have children ..... ☐

7. Please indicate how you live (Please tick only one box)

I live alone ..... ☐

I live with my spouse/boy-/ girlfriend ..... ☐

I live with one or both of my parents ..... ☐

I live in a shared accomodation/dormitory ..... ☐

I live in an aassisted living facility... ..... ☐

Other, please specify: _____

8. Do you have one or more friends? ..... Yes ☐ No ☐

9. Do you have a good relationship with your family? ..... Yes ☐ No ☐

Education and Employment

10. **What is the highest education you have completed?** (Please tick only one box)

Primary school for 8 years or fewer years ☐
Primary school (9th grade) ☐
Expanded primary school (10th grade) ☐
Vocational practical basic course
(e.g. Technical school /crafts education (HG/EFG) ☐
General secondary education
(E.g. High school/HF) ☐
Vocational upper secondary education (HHX/HTX) ☐
Short tertiary education (less than 3 years) ☐
Medium long tertiary education (3-4 years) ☐
Long tertiary education (over 4 years) ☐

Other, please specify: _____

11. **Which of the following statements, best describes your work?**
(Please read the list carefully and tick only one box)

Working full-time ☐
Working part-time
(including those with part-time pension) ☐
Self-employed ☐
Freelancer ☐
Employed with wage subsidies in a private or public company ☐
Unemployed ☐
On leave ☐
Rehabilitation ☐
Receiving sickness benefits ☐
Receiving early retirement benefits ☐
Stay-at-home mom/dad ☐
Student, trainee or apprentice ☐
Job with special support ☐
Retirement ☐

Other, please specify: _____

12. What is your job title? _____

13. How many hours do you work per week? ☐☐ hours

14. Do you need help finding a job? Yes ☐ No ☐

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Neurofibromatosis

15. How old were you when you received the diagnosis ..... ☐☐ years

16. Do other members in your family who have NF1?

No, no other family member has NF1 ..... ☐

My mother has NF1 ..... ☐

My father has NF1 ..... ☐

My sister has NF1 ..... ☐

My brother has NF1 ..... ☐

Others, please specify who: _____

17. Do you regularly take prescritption medication? ..... Yes ☐ No ☐

If yes, please specify Medication name here: _____ Dose: _____

_____ Dose: _____

_____ Dose: _____

_____ Dose: _____

A Symptoms of Neurofibromatosis

For each question, please choose which of the following symptoms of neurofibromatosis you either have or have had.

1. Have you ever had symptoms of neurofibromatosis, which makes the disease visible to others?

Yes ☐
No ☐

2. How many café-au-lait spots do you have?

None ☐
More than 5 ☐
6 or more ☐

3. Where do you have café-au-lait spots?

I have none ☐
In the face? ☐
On the body ☐
Both, in the face and on the body ☐

4. How many neurofibromas do you have?

None ☐
1 ☐
2 or more ☐

5. Where do you have neurofibromas? (You can tick several boxes)

I have none ☐
On the skin in the face ☐
On the skin on the hands ☐
On the skin of other parts of the body ☐
Under the skin or deep in the body ☐

6. Do you feel that the neurofibromas affects your wellbeing?

Yes ☐
No ☐
I have none ☐

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7.Do you have a tumor on the optic nerve?

Yes ..... ☐

No ..... ☐

8Have you experienced cramps?

Yes ..... ☐

No ..... ☐

9. Have you received treatment for high blood presure?

Yes ..... ☐

No ..... ☐

10. Have you had tumors in your brain?

Yes ..... ☐

No ..... ☐

11. Have you received treatment for cancer?

Yes ..... ☐

No ..... ☐

12. Do you feel that you have significant health problems?

Yes ..... ☐

No ..... ☐

13. Do you feel that your health problems are treatable?

Yes ..... ☐

No ..... ☐

B Visability of neurofibromatosis

Please state what fits best for you:

1. If you have neurofibromas on the face or on the hands, are there

5 or less neurofibromas ..... ☐

More than 5 neurofibromas ..... ☐

2. Are your neurofibromas visible when you are wearing clothes?

Yes ..... ☐

No ..... ☐

3. Do you have scoliosis?

Yes ..... ☐

No ..... ☐

4. Do you feel that your gait and posture look different from other people?

Yes ..... ☐

No ..... ☐

5. Do you have tumors on the optic nerve?

Yes ..... ☐

No ..... ☐

6. If you have tumors on the optic nerve, does it affect your vision?

Yes ..... ☐

No ..... ☐

C Problems regarding neurofibromatosis

DIRECTIONS
Adults with Neurofibromatosis Type 1 sometimes have special problems.
Please tell us how much of a problem each one has been for you during the past ONE month by circling. There are no right or wrong answers. If you do not understand a question, please ask for help. (Put only one X for each question)

In the past **ONE month**, how much of a problem has this been for you ..

	Never	Almost never	Sometimes	Often	Almost always
PHYSICAL FUNCTIONING (problems with...)					
1. Feeling physically weak	☐	☐	☐	☐	☐
2. Walking more than one block	☐	☐	☐	☐	☐
3. Climbing stairs	☐	☐	☐	☐	☐
4. Running	☐	☐	☐	☐	☐
5. Doing a sports activity or exercise	☐	☐	☐	☐	☐
6. Lifting something heavy	☐	☐	☐	☐	☐
7. Doing chores around the house	☐	☐	☐	☐	☐
EMOTIONAL FUNCTIONING (problems with...)					
8. Feeling anxious	☐	☐	☐	☐	☐
9. Feeling sad	☐	☐	☐	☐	☐
10. Feeling angry	☐	☐	☐	☐	☐
11. Feeling frustrated	☐	☐	☐	☐	☐
12. Feeling helpless or hopeless	☐	☐	☐	☐	☐
SOCIAL FUNCTIONING (problems with...)					
13. Getting support from others	☐	☐	☐	☐	☐
14. Having enough energy for social activities	☐	☐	☐	☐	☐

In the past **ONE month**, how much of a problem has this been for you ..

	Never	Almost never	Sometimes	Often	Almost Always
COGNITIVE FUNCTIONING (problems with ...)					
15.Keeping attention on things	☐	☐	☐	☐	☐
16. Remembering what people tell you	☐	☐	☐	☐	☐
17. Remembering what you just heard/read	☐	☐	☐	☐	☐
18. Thinking quickly	☐	☐	☐	☐	☐
19. Remembering what you were just thinking	☐	☐	☐	☐	☐
COMMUNICATION (problems with...)					
20.Telling the doctors and nurses how you feel	☐	☐	☐	☐	☐
21. Asking the doctors and nurses questions	☐	☐	☐	☐	☐
22. Talking with others about your disorder	☐	☐	☐	☐	☐
WORRY (problems with...)					
23. Worrying about my neurofibromas	☐	☐	☐	☐	☐
24. Worrying about side effects from medical treatments	☐	☐	☐	☐	☐
25. Worrying about whether or not medical treatments are working	☐	☐	☐	☐	☐
26. Worrying that neurofibromas will grow bigger or reoccur	☐	☐	☐	☐	☐
27. Worrying about my future or the risk of having children with Neurofibromatosis Type 1	☐	☐	☐	☐	☐
28. Worrying about the risk of other health related issues associated with Neurofibromatosis Type 1	☐	☐	☐	☐	☐
PERCEIVED PHYSICAL APPEARANCE (Problems with...)					
29. Feeling that I am not good looking	☐	☐	☐	☐	☐
30. Not wanting other people to see my neurofibromas	☐	☐	☐	☐	☐
31. Being embarrassed about others seeing my body	☐	☐	☐	☐	☐

In the past **ONE month**, how much of a **problem** has this been for you ...

	Never	Almost Never	Sometimes	Often	Almost Always
PAIN AND HURT (problemer with...)					
32. Aching or hurting	☐	☐	☐	☐	☐
33. Aching or hurting a lot	☐	☐	☐	☐	☐
34. Not sleeping because of pain	☐	☐	☐	☐	☐
PARESTHESIAS (problems with...)					
35. A burning sensation in some part of my body	☐	☐	☐	☐	☐
36. A tingling sensation in some part of my body	☐	☐	☐	☐	☐
SKIN IRRITATION (problems with ...)					
37. Itching	☐	☐	☐	☐	☐
38. Itching a lot	☐	☐	☐	☐	☐
39. Getting a skin rash when exposed to sun	☐	☐	☐	☐	☐
40. Tolerating temperature changes ..	☐	☐	☐	☐	☐
41. Rough skin	☐	☐	☐	☐	☐
Sensation (problems with...)					
42. Vision in one or both eyes	☐	☐	☐	☐	☐
43. Seeing well enough with glasses or contact lenses	☐	☐	☐	☐	☐
44. Hearing in one or both ears	☐	☐	☐	☐	☐
45. Speech	☐	☐	☐	☐	☐
MOVEMENT AND BALANCE (problems with...)					
46. Bending my body	☐	☐	☐	☐	☐
47. Moving one or both legs	☐	☐	☐	☐	☐
48. Using or moving one or both arms	☐	☐	☐	☐	☐
49. Keeping balance when sitting or standing	☐	☐	☐	☐	☐

In the past ONE month, how much of a problem has this been for you …

	Never	Almost never	Sometimes	Often	Almost always
DAILY ACTIVITIES (problems with...)					
50. Putting on shoes	☐	☐	☐	☐	☐
51. Buttoning my shirt	☐	☐	☐	☐	☐
52. Combing my hair	☐	☐	☐	☐	☐
53. Getting into the bathroom to use the toilet	☐	☐	☐	☐	☐
54. Undressing to use the toilet	☐	☐	☐	☐	☐
55. Getting in and out of bathtub or shower	☐	☐	☐	☐	☐
56. Brushing my teeth	☐	☐	☐	☐	☐
57. Eating with a fork and knife	☐	☐	☐	☐	☐
58. Using a phone	☐	☐	☐	☐	☐
59. Shopping	☐	☐	☐	☐	☐
60. Managing money	☐	☐	☐	☐	☐
61. Driving	☐	☐	☐	☐	☐
FATIGUE (problems with...)					
62. Feeling tired	☐	☐	☐	☐	☐
63. Resting a lot	☐	☐	☐	☐	☐
64. Having enough energy to do things that I like to do	☐	☐	☐	☐	☐
TREATMENT ANXIETY (problems with...)					
65. Getting scared about going to the doctor	☐	☐	☐	☐	☐
66. Getting scared about going to the hospital	☐	☐	☐	☐	☐
67. Being responsible for my medicines or therapy	☐	☐	☐	☐	☐
SEXUAL FUNCTIONING (problems with...)					
68. Fatigue or lack of energy affecting your satisfaction with your sex life	☐	☐	☐	☐	☐
69. Pain affecting your satisfaction with your sex life	☐	☐	☐	☐	☐
70. Ability to have children with a fertile partner	☐	☐	☐	☐	☐

D Memory and concentration

Please answer the questions below, rating yourself on each of the criteria shown using the scale on the right side of the page. As you answer each question, place an X in the box that best describes how you have felt and conducted yourself over the past 6 months. (Please tick one box only per question)

	Never	Rarely	Sometimes	Often	Very often
1. How often do you have trouble wrapping up the final details of a project, once the challenging parts have been done?	☐	☐	☐	☐	☐
2. How often do you have difficulty getting things in order when you have to do a task that requires organization?	☐	☐	☐	☐	☐
3. How often do you have problems remembering appointments or obligations?...	☐	☐	☐	☐	☐
4. When you have a task that requires a lot of thought, how often do you avoid or delay getting started?...	☐	☐	☐	☐	☐
5. How often do you fidget or squirm with your hands or feet when you have to sit down for a long time?	☐	☐	☐	☐	☐
6. How often do you feel overly active and compelled to do things, like you were driven by a motor?	☐	☐	☐	☐	☐
7. How often do you make careless mistakes when you have to work on a boring or difficult project?	☐	☐	☐	☐	☐
8. How often do you have difficulty keeping your attention when you are doing boring or repetitive work?	☐	☐	☐	☐	☐
9. How often do you have difficulty concentrating on what people say to you, even when they are speaking to you directly?	☐	☐	☐	☐	☐
10. How often do you misplace or have difficulty finding things at home or at work?	☐	☐	☐	☐	☐
11. How often are you distracted by activity or noise around you?.....	☐	☐	☐	☐	☐
12. How often do you leave your seat in meetings or other situations in which you are expected to remain seated?	☐	☐	☐	☐	☐
13. How often do you feel restless or fidgety?.....	☐	☐	☐	☐	☐
14. How often do you have difficulty unwinding and relaxing when you have time to yourself?	☐	☐	☐	☐	☐
15. How often do you find yourself talking too much when you are in social situations?	☐	☐	☐	☐	☐
16. When you're in a conversation, how often do you find yourself finishing the sentences of the people you are talking to, before they can finish them themselves?	☐	☐	☐	☐	☐
17. How often do you have difficulty waiting your turn in situations when turn taking is required?	☐	☐	☐	☐	☐
18. How often do you interrupt others when they are busy?	☐	☐	☐	☐	☐

E Worrying

Over the last 2 weeks, how often have you been bothered by the following problems? (Use "X" to indicate your answer).

	Not at all	Several days	More than half the days	Nearly every day
1. Feeling nervous, anxious or on edge	☐	☐	☐	☐
2. Not being able to stop or control worrying	☐	☐	☐	☐
3. Worrying too much about different things	☐	☐	☐	☐
4. Trouble relaxing	☐	☐	☐	☐
5. Being so restless that it is hard to sit still	☐	☐	☐	☐
6. Becoming easily annoyed or irritable	☐	☐	☐	☐
7. Feeling afraid as if something awful might happen	☐	☐	☐	☐

F Your mood

Over the last 2 weeks, how often have you been bothered by any of the following problems? (Use "X" to indicate your answer)	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	☐	☐	☐	☐
2. Feeling down, depressed, or hopeless	☐	☐	☐	☐
3. Trouble falling or staying asleep, or sleeping too much	☐	☐	☐	☐
4. Feeling tired or having little energy	☐	☐	☐	☐
5. Poor appetite or overeating	☐	☐	☐	☐
6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down	☐	☐	☐	☐
7. Trouble concentrating on things, such as reading the newspaper or watching television	☐	☐	☐	☐
8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	☐	☐	☐	☐
9. Thoughts that you would be better off dead or of hurting yourself in some way	☐	☐	☐	☐

10. If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all ..... ☐
Somewhat difficult ..... ☐
Very difficult ..... ☐
Extremely difficult ..... ☐

G FATIGUE

Instructions:
By means of the following statements we would like to get an idea of how you have been feeling lately. There is for example the statement : "I Feel relaxed"

If you think that this is entirely true, that indeed you have been feeling relaxed lately please place an X in the extreme left box; like this : ..... yes , that is true ☒ ☐ ☐ ☐ ☐ no, that is not true

The more you disagree with the statement, the more you can place an X in the direction of "no, that is not true". Please do not miss out a statement and place only one X in a box for each statement.

1. Physically, I feel only able to do a little ..... yes, that is true ☐ ☐ ☐ ☐ ☐ no, that is not true
2. I feel very active ..... yes, that is true ☐ ☐ ☐ ☐ ☐ no, that is not true
3. I think I do a lot in a day ..... yes, that is true ☐ ☐ ☐ ☐ ☐ no, that is not true
4. When I am doing somthing, I can keep my thought on it ..... yes, that is true ☐ ☐ ☐ ☐ ☐ no, that is not true
5. Physically I can take on a lot ..... yes, that is true ☐ ☐ ☐ ☐ ☐ no, that is not true
6. I think I do very little in a day ..... yes, that is true ☐ ☐ ☐ ☐ ☐ no, that is not true
7. I can concentrate well ..... yes, that is true ☐ ☐ ☐ ☐ ☐ no, that is not true
8. It takes a lot of effort to concentrate on things ..... yes, that is true ☐ ☐ ☐ ☐ ☐ no, that is not true
9. Physically I feel I am in a bad condition..... yes, that is true ☐ ☐ ☐ ☐ ☐ no, that is not true
10. I get little done ..... yes, that is true ☐ ☐ ☐ ☐ ☐ no, that is not true
11. My thoughts easily wander, ... yes, that is true ☐ ☐ ☐ ☐ ☐ no, that is not true
12. Physically I feel I am in an excellent condition ... yes, that is true ☐ ☐ ☐ ☐ ☐ no, that is not true

H The following questions address need for support

People have different needs for support. A lot of people receive help and support from family and friends, but here we are interested in knowing whether you need professional help or support. Please state on which level the following statements apply to you.
(Please tick only one box per for each question)

Up till now, i have needed...	Not at all	At a low level	To some degree	Very much
1. help to deal with physical probelms	☐	☐	☐	☐
2. help to deal with family related problems	☐	☐	☐	☐
3. psychological support	☐	☐	☐	☐
4. help to deal with sexual problems	☐	☐	☐	☐
5. help to deal with work related problems	☐	☐	☐	☐
6. help to deal with economic problems	☐	☐	☐	☐

To date my needs **have been fulfilled in.....** (Please mark as 'not relevant' if you did not need help)	Not at all	At a low level	To some degree	I høj grad	Not relevant
7. help to deal with physical problems	☐	☐	☐	☐	☐
8. help to deal with family related problems	☐	☐	☐	☐	☐
9. psychological support	☐	☐	☐	☐	☐
10.help to deal with sexual problems	☐	☐	☐	☐	☐
11.help to deal with work related problems	☐	☐	☐	☐	☐
12.help to deal with economic problems	☐	☐	☐	☐	☐

Do you have other problems related to neurofibromatosis 1
that you think are not covered by the previous questions? ..... Yes ☐ No ☐

If yes, please describe what kind and how:

If you have other comments, you are welcome to describe them here.

Thank you for your help!

Please use the enclosed envelop to send
back the questionnaire.

life with NF1

Research project on life with neurofibromatosis –NF1

Please, sign this consent form if you wish to participate in the project

Declaration from participant:

- I have read "Information to participants" about the research project "Life with neurofibromatosis – NF1".
- I wish to participate in the study and understand that it is entirely voluntary and that I can withdraw my consent to participate at any time.
- I give permission to collect information regarding my health from medical journals and registries for the purpose of this study.
- I give permission to be invited for an interview about concentration and memory. It is voluntary to choose to participate in this interview.
- The collected information will only be used for research purposes. The researchers have a duty of confidentiality, and the results will only be published as statistics; individual answers are not identifiable.
- Information about my health as well as other confidential information may be forwarded to persons who administer a compulsory quality control of the research study.

I hereby give my consent to the above.

Name of participant:_____

Date:_____ Signature:_____

Would you like to receive a short description of the results of the investigation?

☐ Yes
☐ No

E-mail:_____

Please, return this consent form and the questionnaire using the enclosed pre-paid return envelope. Thank you.

The study is funded by:
Department of Defense, U.S. Army Medical Research and Material Command
Congressionally Directed Medical Research Programs
2013 Neurofibromatosis Research Program

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life with NF1

Date

Name and adress

Center for Kræftforskning
Livet efter kræft

Strandboulevarden 49
2100 København Ø

Tlf +45 3525 7500
Fax +45 3527 1811
www.cancer.dk

UNDER PROTEKTION AF
HENDES MAJESTÆT DRONNINGEN

Invitation to participate in an interview as part of the research project
Life with neurofibromatosis NF1

Dear XX,

We are very grateful that you have participated in the questionnaire study *Life with neurofibromatosis NF1*. We now wish to gain further knowledge on memory, concentration and intelligence. Therefore, we would like to invite you to participate in an interview. We hope this study can bring knowledge to the health care system and the municipalities that can contribute to improving the support offered to adults with NF1 both in getting an education or in finding or keeping a job.

What does it imply to participate in the study?
Please, read "Information to participants", and sign the consent form and return it to us in the enclosed pre-paid envelope **before xx.xx.2016.** Our project assistant Doris Shannon Rohrer will then contact you by telephone or e-mail. Together you can arrange a time and a place for the interview to take place.

Do you have questions?
Please, contact project assistant Doris Shannon Rohrer, phone 3525 7650 (Monday to Wednesday 11:00 AM-2:00 PM) or by e-mail: dsr@cancer.dk

Thank you in advance for your help.

Yours sincerely,

Karoline Doser, PhD student
Pernille Bidstrup, senior researcher, psychologist, PhD
Jeanette Winther, principal investigator, Consultant, MD, DMSc
Danish Cancer Society Research Center

The study is performed in close collaboration with:

Center for Rare Disease, Rigshospitalet	**Center for Rare Disease, Aarhus University hospital**	**NF Organization**
Hanne Hove	John Rosendahl Østergaard	Lene Lind, Chairman
Consultant, MD	Professor, Consultant, MD	www.nfdanmark.dk

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life with NF1

Date

Name and adress

Center for Kræftforskning
Livet efter kræft

Strandboulevarden 49
2100 København Ø

Tlf +45 3525 7500
Fax +45 3527 1811
www.cancer.dk

UNDER PROTEKTION AF
HENDES MAJESTÆT DRONNINGEN

Invitation to healthy persons to participate in a interview as part of the research project *Life with neurofibromatosis NF1*

Dear XX,

We kindly ask for your help with the study *Life with neurofibromatosis NF1* where we gather information on the daily life of adults with NF1 and the problems they may face in relation to memory, intelligence and concentration. NF1 is a genetic disease that gives patients physical symptoms, such as tumors under the skin, but the patients may also experience difficulties with concentration and memory. Therefore, we do interviews with adults with NF1 as well as with healthy persons without NF1 to act as a comparison group.

We would like to invite you as a person without NF1 to participate in an interview. We hope this study can bring knowledge to the patients, the health care system and the municipalities that can contribute to improving the support to adults with NF1 both in getting an education or in finding or keeping a job.

What does it imply to participate in the study?
Please, read "Information to participants", and fill in and sign the consent form and return it to us in the enclosed pre-paid envelope **before xx.xx.2016.** Our project assistant Doris Shannon Rohrer will then contact you by telephone or e-mail. You can then arrange a time and place for the interview to take place.

Do you have questions?
Please, contact project assistant Doris Shannon Rohrer, phone 3525 7650 (Monday to Wednesday 11:00 AM-2:00 PM) or by e-mail: dsr@cancer.dk

Thank you in advance for your help.

Yours sincerely,

Karoline Doser, PhD student
Pernille Bidstrup, senior researcher, psychologist, PhD
Jeanette Winther, principal investigator, Consultant, MD, DMSc
Danish Cancer Society Research Center

The study is performed in close collaboration with:

Center for Rare Disease, Rigshospitalet	**Center for Rare Disease, Aarhus University hospital**	**NF Organization**
Hanne Hove, Consultant, MD	John Rosendahl Østergaard Professor, Consultant, MD	Lene Lind, Chairman www.nfdanmark.dk

Information to participants

life with NF1

Information to participants on the research project *Life with neurofibromatosis – NF1*

Interview on memory and concentration


Jeanette


Doris


Pernille


Karoline

life with NF1

We sincerely thank you for your participation in the questionnaire study *Life with neurofibromatosis NF1*.

We would now like to gain further knowledge on memory, concentration and intelligence in adults with NF1. Therefore, we would like to invite you to participate in an interview.

We anticipate that the health care system and the municipality can use this knowledge to support adults with NF1 in getting an education or in finding or keeping a job.

Before you make a decision you can read about the study and why we are conducting it on the following pages.

Investigators

Jeanette Falck Winther
Principal investigator, Consultant, MD, DMSc

Doris Shannon Rohrer
Project assistant

Pernille Bidstrup
Senior researcher, psychologist, PhD,

Karoline Doser
PhD student

Danish Cancer Society Research Center

Participation in the interview
First, we kindly ask you to read and sign the informed consent form and return it to us using the enclosed pre-paid envelope. Our project assistant will subsequently contact you by phone or e-mail to arrange a time and a place for the interview. You may choose to have the interview take place in your home, or at the Center for Rare Disease in Aarhus.

Interview

- The interview takes around two hours and will be in three parts with short breaks in between.
- Topics will include memory, concentration, intelligence, language, planning of activities and socializing with family and friends.
- The interview will include a questionnaire and doing some paper-based and IPad-based tasks together with us.

Voluntary participation
Participation in the study is voluntary. You can withdraw from the study at any time without giving a reason or explanation. Your ongoing treatment will not be affected whether you choose to participate or not.

All information given will be treated with full confidentiality, and all staff working on the project has a duty of confidentiality. Information about your health as well as other confidential information may be forwarded to persons who administer a compulsory quality control of the research study. The project is approved by the Danish Data Protection Agency (jr.nr: 2014-41-2935) which means it fulfills all requirements by the Danish State concerning data protection.

Results of the study
We cannot give you information about your own study results, but if you are interested, we can send you a brief summary of the overall study results. We will ask about that on the consent form.

Travel expenses
If you decide to participate in the interview at a different place than your home, your travel expenses will be reimbursed. You just hand in your original receipts, and the money will be transferred to your bank account.

Honorarium
We offer a honorarium of 500 DKK for your participation. The amount is subject to taxation through your CPR-number.

If you have any questions about the study, please contact our project assistant:

Doris Shannon Rohrer
Danish Cancer Society Research Center
Strandboulevarden 49
2100 København Ø

Telephone: 35257650
Monday-Wednesday
11:00 AM-2:00 PM
e-mail: dsr@cancer.dk

Funding
The research project is funded by:

Department of Defense
U.S. Army Medical Research and Materiel Command
Congressionally Directed Medical Research Programs
2013 Neurofibromatosis Research Program

Life with Neurofibromatosis – NF1

Who is behind the study?
Jeanette Falck Winther,
Principal investigator
Consultant, MD, DMSc
Danish Cancer Society Research Center

Collaborators

Danish Cancer Society Research Center
Karoline Doser
PhD student

Pernille Bidstrup,
Senior researcher, psychologist, PhD,

Susanne Dalton,
Senior researcher, MD, PhD

Christoffer Johansen,
Professor, Consultant, MD, DMSc

Center for Rare Disease
Rigshospitalet
Hanne Hove, Consultant, MD

Center for Rare Disease
Aarhus University Hospital
John Rosendahl Østergaard
Professor, Consultant, MD

NF Organization
Lene Lind, chairman
www.nfdanmark.dk

Research unit, Psychiatric Center Glostrup &
Children and Youth Psychiatric Center,
Capital Region of Denmark
Jens Richardt Møllegaard Jepsen,
Senior researcher, psychologist, PhD

life with NF1

Research project on life with neurofibromatosis - NF1
Interview on memory and concentration

Please, sign this consent form if you wish to participate in the project

Declaration from participant:

- I have read "Information to participants" about the research project "Life with neurofibromatosis – NF1".
- I wish to participate in the study and understand that it is entirely voluntary and that I can withdraw my consent to participate at any time.
- I give permission to collect information about my health from health records and registers for the purpose of this study.
- The collected information will only be used for research purposes. The researchers have a duty of confidentiality, and the results will only be published as statistics; individual answers are not identifiable.
- Information about my health as well as other confidential information may be forwarded to persons who administer a compulsory quality control of the research study.

I hereby give my consent to the above.

Name of participant:_____

Date:_____ Signature:_____

Would you like to receive a short description of the results of the investigation?

☐ Yes
☐ No

E-mail:_____

Please, return this consent form using the enclosed pre-paid return envelope. Thank you.

The study is funded by:
Department of Defense, U.S. Army Medical Research and Material Command
Congressionally Directed Medical Research Programs
2013 Neurofibromatosis Research Program

Power calculation

Study 7. Cognitive functioning and need for professional support among adults with NF1

This study based on neuro-psychological assessments will include a NF1 patient sample of n=100 and a healthy control group of n=50 matched by gender and age.
Both patients and controls will be tested using the same standardized instruments.
Power calculations are included below to illustrate the expected power on a number of key cognitive outcomes obtained using the described sample size.

Mean and standard deviations were based on: *Ferner RE, Hughes R a. C, Weinman J. Intellectual impairment in neurofibromatosis 1. Journal of the Neurological Sciences. 1996. 138(1-2), 125–133.*

		NF1 patients n=103 Mean (SD)	Matched controls n=105 Mean (SD)	Power
Wechsler Adult Intelligence Scale (WAIS-IV)	Block design (subtest score)	7.9 (2.9)	10.4 (2.9)	0.99
	Digit Symbol-Coding (processing speed) (subtest score)	6.8 (2.9)	9.4 (2.9)	0.99
	MEAN IQ full scale	88.6 (14.6)	101.6 (14.2)	0.99
	Immediate recall (subtest score)	4.1 (1.9)	5.1 (2.1)	0.99
The Stroop test (reaction time)	mean error (%)	2.66 (3.88)	1.24 (1.8)	0.99

The power calculations indicate that the sample size of 100 patients and 50 healthy controls is sufficient and that we will have a power of 99% to detect the described differences between the two samples.

Literature overview academic impairments & educational attainment

Study (year)	Design	Sample size (N)	Sample characteristics	Aim	Measures, source of obtained data	Statistical Methods	Results	Conclusion
(Watt, Shores, & North, 2008) Australia	Original study,	N=30 children	Mean age 9.29 years (SD=1.32), severity based on Riccardi scale: majority mild, N=3 with ADHD	To examine the reading skills	Castles Word/Non-word test, Neuropsychological Test battery (e-g. WISC-IV)	Descriptive analysis Regression analysis	All participants demonstrated a normal level of general intellectual functioning. 67% demonstrated deficits in reading skills, of them 75% met criteria for phonological dyslexia, 20% mixes dyslexia	The majority of children with NF1 having difficulty employing spelling-to-sound rules to assemble a pronunciation when reading.
(Cutting & Levine, 2010) USA	Original study Control group	NF1-RD N=13 NF1 N=12 IRD N=33 Control N=36 children	NF1-RD age10.31 (SD=2.17) NF1 age9,26 (SD=2.13) IRD age 9.33 (SD=1.18) Control age9.59 (SD= 2.30)	To examine the cognitive profile of children with NF1with and with our reading disabilities compared with children with idiopathic reading disorders and typically developed readers (controls)	Reading related measures Reading comprehension measures Oral language measures Visual spatial measure Weehsler intelligence battery for children ADHD diagnosis	MANOVA, Covarying for ADHD symptoms, Examining group differences	NF+RD significant lower level in IQ than control Children with NF1+RD performed similarly to children with IRD on phonological, rapid naming and reading comprehension measures. Children with NF1+RD displayed pronounced visual-spatial deficits compared to IRD and control group	Overall, findings suggest that a more refined classification of children with NF-1 may be helpful for tailoring academic interventions.
(Krab et al., 2008) Netherlands	Original study, cross-sectional	N=86 children	Mean age 11.9 (2.5)Age range (7-17 years), 54.7% male Riccardi minimal (30), mild (30), moderate (25), severe (1), using ADHD medication n=14	To determine the impact of NF1 on school performance	WISC IV Rey Auditory verbal learning Rey Complex figure Peabody Picture Vocabulary Test III Boston Naming Test Trail making test Wisconsin Card Sorting Test Stroop Color word-test	ANAOVA, Chi-square, K-S test for normality	Only 10% of NF1 did not show any school-functioning problems. Severity of NF1 correlated with the cognitive deficits, 75% performed more than 1 standard deviation below peers in at least one of the domains of spelling, math, technical reading or comprehensive reading. 4x increased risk of attending special education and 6x increased risk for receiving remedial teaching for learning, behavior, speech or motor problems.	NF1 has profound impact on school performance
(Coudé, Mignot, Lyonnet, & Munnich, 2006) France	Original study, Control group	Children with NF1 n=116 Typically developed children N=80	NF1: mean age 12.4 years, SD=2.3, range 6-20 years, 62 males, 54 females TDC: mean age 11.5 SD=2.0, range 6-20, 46 males, 34 females	To investigate the occurrence and specificity of academic impairment in French children with NF1	Registered complications, Registered repetitions of school grade	Descriptive statistics Chi-square	70 of 116 patients had significant learning impairment (one or more grade repetitions or school exclusion)	
(Gilboa, Rosenblum, Fattal-Valevski, Toledano-Alhadef, & Josman, 2014) Israel	Original study Control group	Children with NF1 n=29 Matched typically developed children n=27	Age range 8-16 years, NF1 8 male, 21 female, mean age 12.3 (SD=2.6), mean estimated IQ score 98.96 (SD=12.77), 5 children diagnosed with ADHD Controls 8 males, 19 female, mean age 12.4 (SD=2.5),m estimated IQ 107.19 (SD=12.08)	To compare the executive function of children with NF1 to typically developing children, and to investigate whether those abilities could predict the child's academic success in terms of academic skills and enablers	Assessment of the Dysexecutive Syndrome in Children (BADS-C), BRIEF, Academic Competence Evaluation scales (ACES), WISC-R-95	Correlation analysis Regression analysis	Significant lower performance of NF1 children on subtests of the BADS, initiate, working memory, plan/organize and organizations of materials out of the BRIEF than TDC. Significant correlations and predictive models via regression analysis were generated for BADS; BRIEF and ACES.	Children with NF1 have executive dysfunction that partially accounts for their difficulties in academic achievements.
(Orraca-Castillo, Estévez-Pérez, & Reigosa-Crespo, 2014) Cuba	Original study	Children with NF1 n=32	Age range 7-14 years	To assess basic capacities which are in involved in reading and mathematical achievement.	Neurocognitive tests: The MAT (Mathematics Attainment Test) and RCAT (Reading and Comprehension Attainment test) Basic Numerical Battery (BNB) Raven's Colored Progressive Matrices (RCPM) test	Generalized linear Models	Deficits in lexical and phonological strategies and poor number facts retrieval were found underlying reading and arithmetic disorders Efficiencies in lexical/phonological strategies and mental arithmetic were significant predictors of individual differences in reading attainment and math. The estimated prevalence of Developmental Dyscalculia (DD) was 18.8%, and the male: female ratio was 5:1. Prevalence of Developmental Dyslexia (DL) was almost 3 times as high (50%), and no gender differences were found	The present study confirmed word decoding deficits and poor number facts retrieval under- lying DL and DD, respectively.

Coudé, F. X., Mignot, C., Lyonnet, S., & Munnich, A. (2006). Academic impairment is the most frequent complication of neurofibromatosis type-1 (NF1) in children. *Behavior Genetics*, *36*(5), 660–664. http://doi.org/10.1007/s10519-005-9040-9

Cutting, L. E., & Levine, T. M. (2010). Cognitive profile of children with neurofibromatosis and reading disabilities. *Child Neuropsychology : A Journal on Normal and Abnormal Development in Childhood and Adolescence*, *16*(5), 417–432. http://doi.org/10.1080/09297041003761985

Gilboa, Y., Rosenblum, S., Fattal-Valevski, A., Toledano-Alhadef, H., & Josman, N. (2014). Is there a relationship between executive functions and academic success in children with neurofibromatosis type 1? *Neuropsychological Rehabilitation*, *2011*(June), 1–18. http://doi.org/10.1080/09602011.2014.920262

Krab, L. C., Aarsen, F. K., de Goede-Bolder, A., Catsman-Berrevoets, C. E., Arts, W. F., Moll, H. A., & Elgersma, Y. (2008). Impact of neurofibromatosis type 1 on school performance. *J Child Neurol*, *23*(9), 1002–1010. http://doi.org/0883073808316366 [pii]10.1177/0883073808316366 [doi]

Orraca-Castillo, M., Estévez-Pérez, N., & Reigosa-Crespo, V. (2014). Neurocognitive profiles of learning disabled children with neurofibromatosis type 1. *Frontiers in Human Neuroscience*, *8*(June), 386. http://doi.org/10.3389/fnhum.2014.00386

Watt, S. E., Shores, A., & North, K. N. (2008). An examination of lexical and sublexical reading skills in children with neurofibromatosis type 1. *Child Neuropsychology : A Journal on Normal and Abnormal Development in Childhood and Adolescence*, *14*(5), 401–418. http://doi.org/10.1080/09297040701595505

7 April 2016

Line Kenborg, MSc, PhD
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Dear Dr. Kenborg,

In consideration of our various correspondences by email and my exchanges with Dr. J.F. Winther, it is my pleasure to invite you to collaborate with me at *The Neurofibromatosis Institute* in the final quarter of 2016. I will afford you the unique resources of TNFI and, as well, facilitate your engagement with Dr. Tena Rosser at L.A. Children's Hospital.

The purposes of our joint and mutual endeavors are to clarify further key elements of the *natural history of NF1*. During the time that you and your family are here, you will have my devoted attention to address the scientific issues of concern. The Danish National NF1 study is so far (over 60 years) very impressive, and collating that material with data from America and other countries will likely benefit many thousands of people worldwide, including those with *and* without NF1.

If, beyond this letter, there is anything I can do to facilitate your travel preparations, please let me know. I very much look forward to our on-site collaboration in this important scientific endeavor.

Sincerely,

V.M. Riccardi

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